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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1643	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/670,472	MA ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11 and 46-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,11 and 47-50* is/are allowed.

6)☒ Claim(s) *46 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed October 7, 2008, is acknowledged and has been entered. Claims 27-31, 33, and 45 have been canceled. Claim 1 has been amended. Claims 47-51 have been added.

2. Claims 1, 11, and 46-51 are pending in the application and are currently under examination.

Election/Restriction

3. The preceding Office action mailed July 22, 2008, failed to note that the restriction of claim 46 has been withdrawn, so as to rejoin the subject matter pertaining to the peptide of SEQ ID NO: 5 of the inventions of Groups 1 and 9, as identified in the Office action mailed December 5, 2005.

Furthermore, the restriction of subject matter of Groups 1, 9, and 25 was withdrawn by the Office action mailed August 10, 2007, though it does not appear that the Examiner noted this fact.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed July 22, 2008.

Grounds of Objection and Rejection Maintained

Specification

5. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort

made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although Applicant may have made a *bona fide* attempt to resolve this deficiency by appropriately amending the specification, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely Tripure™; see, e.g., paragraph [0124] of the published application[1].

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections – 35 U.S.C. § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of claims 46 and 51 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making** an isolated peptide consisting of the amino acid sequence of SEQ ID NO: 5, **does not reasonably provide enablement for using** an isolated peptide consisting of the amino acid sequence of SEQ ID NO: 5, or more particularly for determining if a cell presents an HLA-A2 molecule on its surface by contacting a sample possibly comprising such a cell with the peptide of SEQ ID NO: 5 or a tetramer[2] comprising the peptide, is maintained. The specification does not

[1] U.S. Patent Application Publication No. 2004/0214779-A1.

[2] As noted in the preceding Office action, a *tetramer* is a term of art, which is used to describe a quarternary complex produced by admixing avidin or streptavidin with biotinylated peptide-MHC molecule complexes at a 4:1 ratio, as first described by Altman et al. (*Science*. 1996 Oct 4; **274**: 94-96) (of record). Avidin or streptavidin binds up to four biotin molecules; so when admixed at a 4:1 ratio, four biotinylated peptide-MHC molecule monomers tend to bind to avidin or streptavidin, thus forming the *tetramer*.

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Note: Herein it is presumed that claim 46 will be amended to depend from claim 51, as opposed to claim 45 (canceled).

Applicant's remarks at page 6 of the amendment filed October 7, 2008, are acknowledged and have been carefully considered but not found persuasive to overcome this ground of rejection.

There are two "enablement" requirements set forth under § 112, first paragraph. The specification must both teach how the invention is made, and how is used.

The specification discloses that the peptide of SEQ ID NO: 5 is useful in practicing the process to which claim 46 is directed, namely a process for determining if a cell presents an HLA-A2 molecule on its surface by contacting a sample possibly comprising such a cell with the peptide of SEQ ID NO: 5 or a tetramer comprising the peptide. It does not appear that there is any other asserted use for the peptide.

Having described the peptide to which claim 51 is directed as consisting of the amino acid sequence of SEQ ID NO: 5 would reasonably enable the skilled artisan to make the peptide without undue experimentation; but such a description is not sufficient to reasonably the skilled artisan to use the peptide.

In this case, the specification teaches how the peptide of SEQ ID NO: 3 can be used; and although there is an allegation that the peptide of SEQ ID NO: 5 can be used in the same manner, there is no factual evidence that the peptide of SEQ ID NO: 5 specifically binds to HLA-A2, as does the peptide of SEQ ID NO: 3, which is used to identify T cells expressing that particular MHC molecule at their surfaces.

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As discussed in the preceding Office actions the specification fails to show that the peptide of SEQ ID NO: 5, which is a variant of the peptide of SEQ ID NO: 3, binds to HLA-A2.

The peptide of SEQ ID NO: 5 differs from the peptide of SEQ ID NO: 3 by the substitution of the ninth amino acid at the carboxy-terminus of SEQ ID NO: 3 (i.e., valine) by alanine.

As explained in the preceding Office action the prior art teaches the consequence of such variation cannot be predicted; the peptide of SEQ ID NO: 5 may retain the ability of the peptide of SEQ ID NO: 3 to bind to HLA-A2, or it may not.

The specification discloses the peptide of SEQ ID NO: 5 is used in the determination that a cell presents an HLA-A2 molecule on its surface, but such a determination can only be made if the peptide binds to HLA-A2 - if the peptide does not bind to HLA-A2, it cannot be used to determine the presence of an HLA-A2 on the surface of a cell. If the peptide of SEQ ID NO: 5 binds to HLA-A2 but does so very

poorly, it is not evident that the peptide can be used to detect the presence of a cell presenting an HLA-A2 molecule on its surface, particularly if the cell presents only one or a few such molecules. Certainly the usefulness of the peptide of SEQ ID NO: 5 hinges upon its affinity for the HLA-A2 molecule.

Ma et al. (*Int. J. Cancer.* 2004; **109**: 698-702) (of record) describes a truncated variant of the peptide of SEQ ID NO: 3, which lacks the carboxyl-terminal valine residue of SEQ ID NO: 3; see entire document (e.g., page 701, Figure 5). This truncated peptide apparently has very little ability to stimulate the specific lysis of target cells by CTL, as compared to the peptide of SEQ ID NO: 3 (page 701, Figure 5), which suggests that the carboxyl-terminal valine residue is critical to the ability of the peptide to bind to HLA-A2 molecules presented at the surface of the target cells.

The specification asserts that the peptide of SEQ ID NO: 5, which lacks this critical residue, is capable of binding to HLA-A2, but fails to provide a showing of any factual evidence in support of such an assertion.

The established peptide-class I MHC binding motif for HLA-A2.1 suggests that for optimal binding affinity, a peptide should be 9 or 10 amino acids long and have a small aliphatic residue (preferably L or M) at the second position from the N-terminus (P2) and at the C-terminus (preferably L or V) (P9 or P10)[3].

Again, the peptide of SEQ ID NO: 5 is a variant of the peptide of SEQ ID NO: 3 in which the *preferred* amino acid at position 9 is replaced by an amino acid that is not generally described as a preferred amino acid in terms of the optimal binding of HLA-A2 by a peptide.

This position is supported by Parker et al. (*J. Immunol.* 1992 Dec 1; **149** (11): 3580-3587); see entire document (e.g., page 3581, Table 1) (of record). Parker describes a variant of a peptide that binds to HLA-A2 in which the amino at the ninth position (i.e., valine) is replaced by alanine; though the original peptide binds to HLA-A2, the variant did not (page 3581, Table 1).

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[3] See, e.g., Parker et al. (*J. Immunol.* 1992 Dec 1; 149 (11): 3580-3587); entire document (e.g., the abstract) (of record).

Thus, the amino acid at 9th position of the nine amino acid peptide (a so-called *anchor* residue) is of prime importance in determining its ability to bind to HLA-A2. The consequence of the substitution of valine by alanine at the ninth position of SEQ ID NO: 3 upon binding to HLA-A2 cannot be predicted, but must be determined empirically.

Accordingly it is submitted that the skilled artisan would not accept the assertion that the peptide of SEQ ID NO: 5 binds to HLA-A2, or that it can be used to determine if a cell present an HLA-A2 on its surface.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), it is submitted that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not have been sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46 is indefinite because the claim depends from claim 45, which has been canceled. The subject matter that is claimed cannot be determined.

Conclusion

10. Claims 1, 11, and 47-50 are allowed; claims 46 and 51 stand rejected.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
January 23, 2009